Influenza Vaccine Production

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Inactivated Influenza Vaccines

- **Trivalent (influenza A H1N1, influenza H3N2, and influenza B); vaccine strains selected to match circulating viruses**
- **Vaccines contain at least 15 μg/dose of each HA (standardized by SRID)**
- **Vaccine Efficacy**
  - **Relates to vaccine potency (immunogenicity)**
  - **Match of vaccine HA (and possibly NA) with circulating strains**
    - **First evidence of reduced vaccine effectiveness because of antigenic drift 2 years after first vaccines licensed for use in United States**
    - **Antigenic drift of HA/NA continuous in influenza A and B viruses**

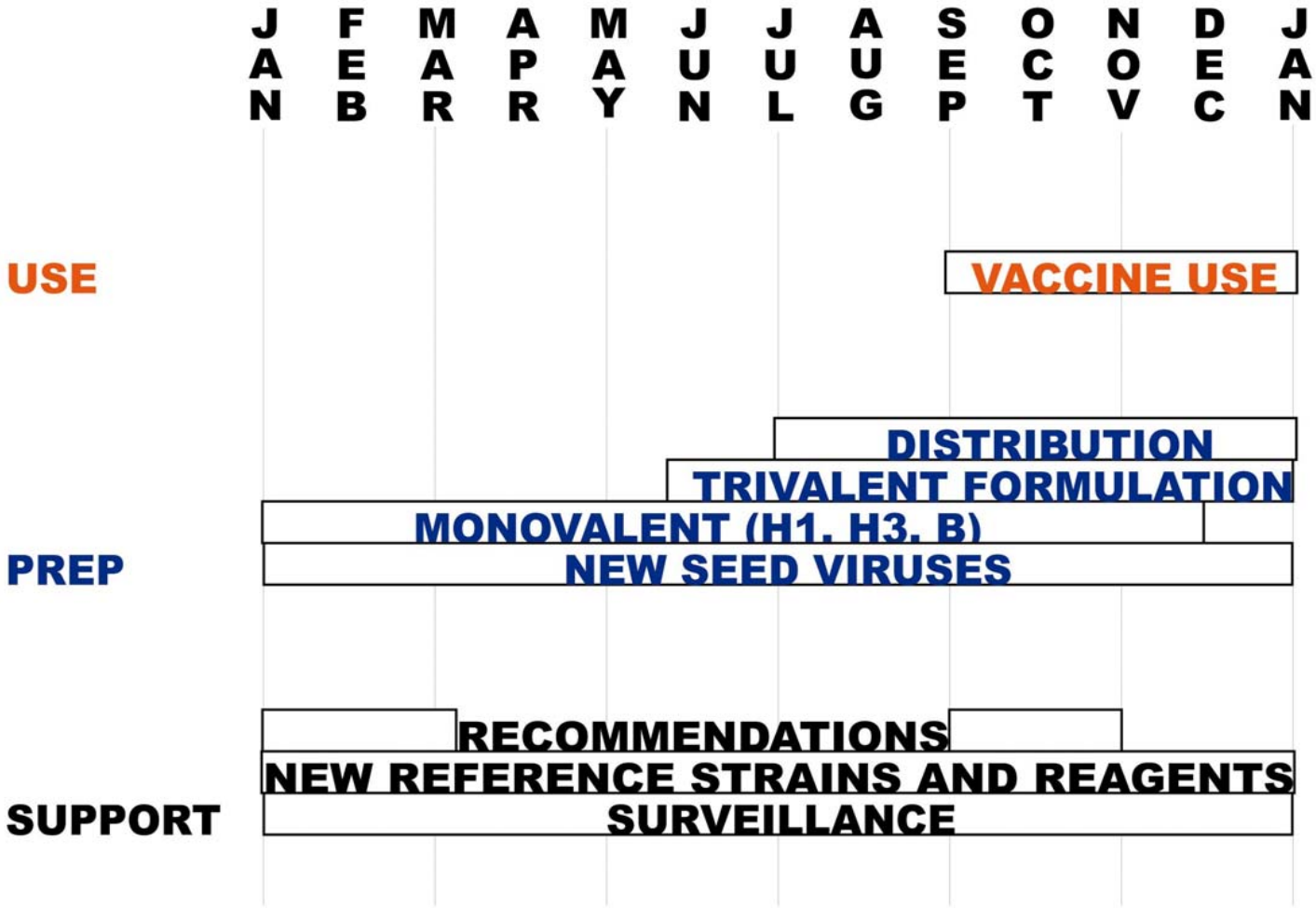
Questions to Be Answered for Strain Changes Every Year

- **Are new (drifted or shifted) influenza viruses present?**
- **Are these new viruses spreading in people?**
- **Do current vaccines induce antibodies against the new viruses (HA)?**
- **Are strains suitable for vaccines available?**

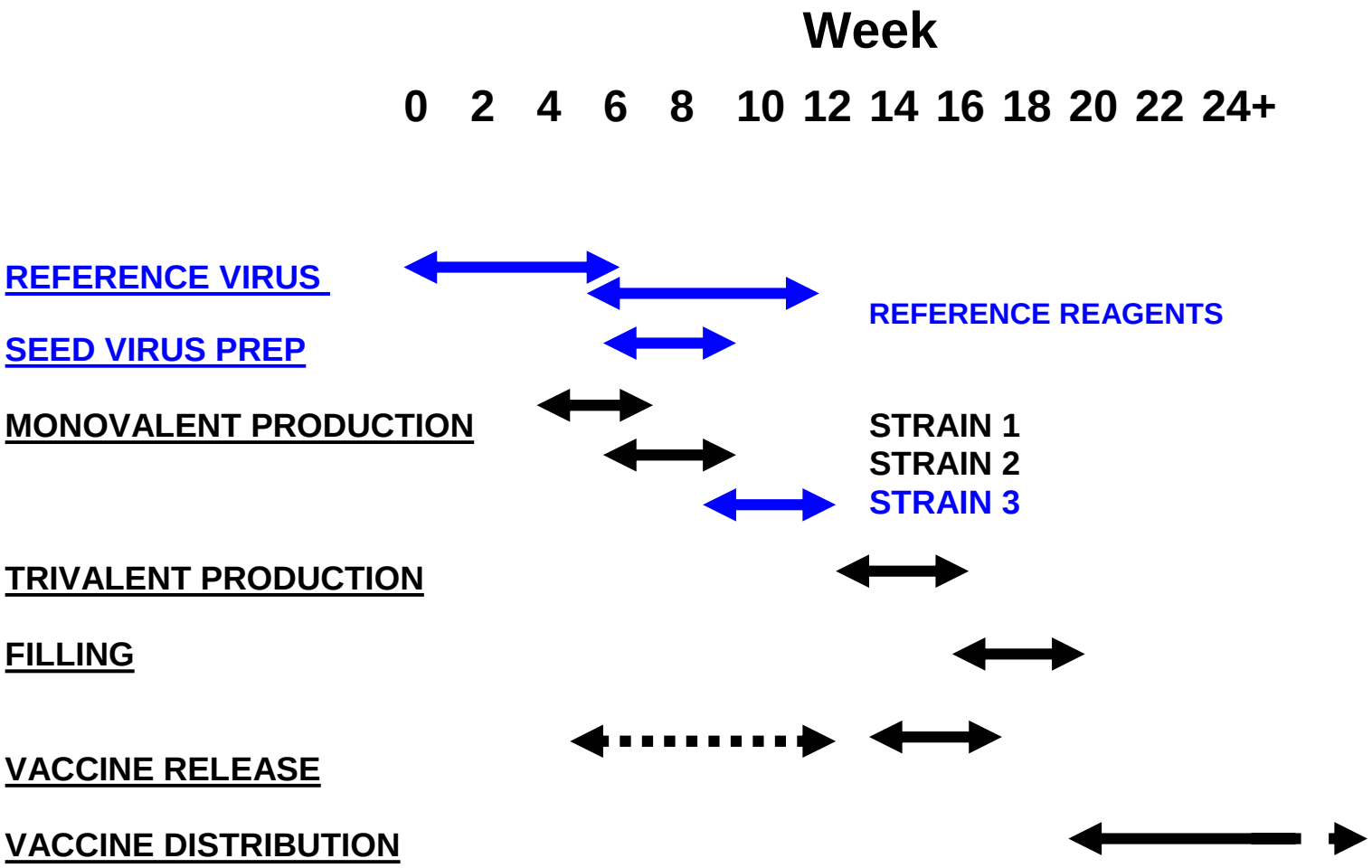
Strains Selected for 2005-2006

- **A/New Caledonia/20/99 (H1N1)-like**
- **A/California/7/2004 (H3N2)-like (***changed from 2004-2005 season)*
  - **A/New York/55/2004**
- **B/Shanghai/361/2002-like**
  - **B/Jilin/20/2003**
  - **B/Jiangsu/10/2003**

Timelines for Vaccine Production



Time to First Trivalent Vaccine Lot after Strain Change



Timing of Production and Distribution

- **Is the FDA (CBER) willing to look at influenza vaccine processes with the intent of finding ways to achieve earlier testing and release of vaccine?**
  - **YES. Changes under consideration include changes to the current procedure for monovalent potency assignment. No changes for trivalent release that will negatively impact release are under consideration for 2006.**
  - **All aspects of our testing/release/support will be periodically re-assessed to ensure twin goals of timely release of vaccine and continued highest standards of product safety, efficacy, potency.**

FDA Resources Devoted to Influenza Vaccine Testing and Release

- **Does the FDA (CBER) have plans to increase the resources devoted to influenza vaccine testing and release in preparation for 2006 season?**
  - **YES (Qualified). Anticipated dedicated new resources for pandemic influenza in FY06 and potentially beyond.**

Early Production of Monovalent Bulks at Risk

- **Does the FDA (CBER) process (test/approve) monovalent bulk lots immediately upon receipt when manufacturers produce lots at risk early in the season?**
  - **YES (Qualified). Early in season (e.g., Jan/Feb), competing demands for serology studies necessary for strain selection.**
    - **In general, there has been no waiting period for monovalent testing, continuous from Feb-Nov**
    - **Under consideration are changes to the current procedure for monovalent potency assignment.**

Production of Monovalent Bulks Using New Viruses or Their High-Growth Reassortants

- **Would limiting the option for vaccine formulation to a single virus for each strain type lead to increased efficiency (e.g., fewer potency reagents)?**
  - **MAYBE. Flexibility important.**
    - **Multiple options provide manufacturers the opportunity to maximize yields in their system**
    - **More diversity of antigens may have positive impact on disease prevention**
    - **Multiple strain options are resource intensive**
    - **No consideration for limiting options at this time**

Production of Potency Reagents

- **Would earlier availability of potency reagents allow earlier formulation and release of vaccine? Can the FDA (CBER) produce potency reagents earlier in the process?**
  - **YES (Qualified). Earlier availability of potency reagents could lead to earlier monvalent potency assignment and trivalent formulation, but in practice this may have minimal effect because of staggered monovalent production.**
  - **UNLIKELY. Antisera production begins when antigen is available. Antigen is available when reference virus is available. High titer antisera requires multiple booster injections.**
  - **MAYBE. Research priorities include investigations into new methods of antigen production and antisera production (e.g., new vectors, concurrent antigen preparation at CBER).**

Size of Vaccine Lots

- **Is increasing the size of lots technically feasible (disadvantages)?**
  - **YES. Feasibility of lot size is a manufacturing issue. In general, CBER has been able to work with various size lots from manufacturers and anticipates being able to do so in the future absent resource limitations.**
    - **Larger lot sizes require pooling of harvests.**
    - **Obvious disadvantage is that any potential problem with a larger monovalent lot impacts a proportionally larger number of vaccine doses.**

Influenza Vaccine Lot Releases

- **Can the FDA (CBER) make any or all of these suggested changes so that the timetable for vaccine availability will shift (late July-early Sept.? Will manufacturers follow suit?**
  - **YES. Changes to monovalent testing procedure under consideration. Investigations into alternative methods to produce reagents a high priority. Investigations into improved test methods a high priority.**
  - **MAYBE. Some aspects of timeline will be difficult to alter, e.g., strain selection process, virus growth characteristics. However, CBER schedules VRBPAC strain selection immediately following WHO meeting to eliminate delay.**
  - **UNKNOWN (but likely).**

Summary

- **Changes in inactivated influenza vaccines occur yearly and are necessary to remain current with circulating viruses.**
- **Timelines for vaccine production are relatively fixed, but CBER will explore all options to expedite without compromises to safety, efficacy, and potency.**
- **CBER is supportive of lengthening the season for which influenza vaccination is recommended in order to maximize vaccine coverage.**
- **CBER is committed to working with manufacturers and our partners in global public health to ensure a safe, effective and adequate supply of vaccine for seasonal and pandemic influenza**